

**UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS**

DANA-FARBER CANCER INSTITUTE,
INC.,

Plaintiff,

v.

ONO PHARMACEUTICAL CO., LTD.,
TASUKU HONJO, E. R. SQUIBB & SONS,
L.L.C., AND BRISTOL-MYERS SQUIBB,
CO.,

Defendants.

Civil Action No. 1:15-cv-13443-MLW

DEFENDANT TASUKU HONJO'S ANSWER

Dr. Tasuku Honjo (“Honjo”) by and through his undersigned counsel, hereby answers the Complaint for correction of inventorship of Dana-Farber Cancer Institute (“Dana-Farber” or “Plaintiff”), in accordance with the numbered paragraphs thereof, as follows. All allegations of fact and conclusions of law contained in the Complaint are denied, except those specifically admitted herein:

Introduction

1. Honjo admits that Dana-Farber purports to have brought an action under 35 U.S.C. § 256 seeking to modify the inventorship of U.S. Patent Nos. 7,595,048 (“the ’048 patent”); 8,168,179 (“the ’179 patent”); 8,728,474 (“the ’474 patent”); 9,067,999 (“the ’999 patent”); and 9,073,994 (“the ’994 patent”) (collectively, the “Patents”). Honjo admits that what purport to be copies of the Patents are attached as Exhibits A through E. Honjo denies that Yoshiko Iwai is currently and Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in this paragraph.

2. Honjo admits the Patents claim a pioneering treatment for cancer using cancer immunotherapy. Honjo admits that cancer immunotherapy is a way to unleash the body's disease-fighting cells, which include the immune system's T lymphocytes, or "T cells," to make a sustained attack on cancer cells. Honjo admits that T cells are a critical component of the body's immune system, recognizing and protecting against viruses and other foreign invaders and also helping to destroy cancer cells. Honjo denies the remaining allegations in Paragraph 2 of the Complaint.

3. Honjo admits that T cells may express a protein called PD-1 on their surface, and that PD-1 serves as an immune system checkpoint. Honjo admits that PD-L1 is a ligand for PD-1. Honjo admits that when PD-L1 on a normal cell binds to PD-1 on a T cell, the effect is to inhibit (or "downregulate") the proliferation of T cells, as well as the T cells' expression of certain immune proteins called cytokines. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 3 of the Complaint, and therefore denies those allegations.

4. Honjo admits that PD-1 was discovered early in the 1990s. Honjo admits that PD-L2 is a second ligand for PD-1. Honjo denies the remaining allegations in Paragraph 4 of the Complaint.

5. Honjo admits that PD-L1 is expressed on certain cancer cells and that PD-L1 can interact with PD-1 on T cells to suppress an immune response against cancer cells, which allows them to live on and multiply while escaping attack from the body's T cells. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 5 of the Complaint, and therefore denies those allegations.

6. Honjo admits that cancer immunotherapy, including the use of antibodies that

block the PD-1 checkpoint pathway, allows a patient's immune system to resume its ability to recognize, attack, and destroy cancer cells. Honjo denies the remaining allegations in Paragraph 6 of the Complaint.

7. Honjo lacks sufficient knowledge or information to form a belief as to Plaintiff's use of a "biological lock and key" analogy, and therefore denies the allegations in Paragraph 7 of the Complaint.

8. Honjo admits that, in 2014, he and Freeman were two of four recipients of the Cancer Research Institutes William B. Coley Award for Distinguished Research in Tumor Immunology and that the prize was stated to be for their "contributions to the discovery of the PD-1 pathway." Honjo denies the remaining allegations in Paragraph 8 of the Complaint.

9. Honjo admits the Patents issued from 2009 to 2015 and contain claims directed to treating cancer with anti-PD-1 antibodies. Honjo admits the Patents list Tasuku Honjo, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama as the inventors of the claimed subject matter. Honjo denies that Shiro Shibayama is or was and Yoshiko Iwai is currently his colleague at Kyoto University. Honjo admits that he worked with Clive Wood at Genetics Institute on the ligand for PD-1, and that Freeman was later included in this work. Honjo denies the remaining allegations in Paragraph 9 of the Complaint.

10. Honjo admits that BMS's anti-PD-1 antibody, Opdivo®, and Merck's anti-PD-1 antibody, Keytruda®, were approved by the FDA in 2014 for the treatment of advanced melanoma. Honjo denies the remaining allegations in Paragraph 10 of the Complaint.

The Parties

11. Honjo lacks sufficient knowledge or information to form a belief as to the allegations in Paragraph 11 of the Complaint, and therefore denies those allegations.

12. Honjo lacks sufficient knowledge or information to form a belief as to the allegations in Paragraph 12 of the Complaint, and therefore denies those allegations.
13. Honjo admits the allegations in Paragraph 13 of the Complaint.
14. Honjo admits the allegations in Paragraph 14 of the Complaint.
15. Honjo denies that he exclusively licensed his rights in the Patents to BMS and Squibb, but he admits that he understands that Ono has done so. Honjo admits the remaining allegations in Paragraph 15 of the Complaint.

16. Honjo admits the allegations in Paragraph 16 of the Complaint.
17. Honjo admits the allegations in Paragraph 17 of the Complaint.

Jurisdiction

18. Honjo admits that the Complaint contends that subject-matter jurisdiction exists over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), and 35 U.S.C. § 256.
19. Honjo denies the allegations in Paragraph 19 of the Complaint.
20. Honjo states that he will not contest that personal jurisdiction exists over BMS and Honjo in the District Court of Massachusetts. Honjo denies the District Court of Massachusetts has personal jurisdiction over Ono.

The Alleged Freeman/Wood/Honjo Collaboration

21. Honjo lacks sufficient knowledge or information to form a belief as to whether Freeman was investigating the “B7” family of proteins in the 1990s, and therefore denies that allegation. Honjo admits the remaining allegations in Paragraph 21 of the Complaint.
22. Honjo lacks sufficient knowledge or information to form a belief as to the allegations in Paragraph 22 of the Complaint, and therefore denies those allegations.

23. Honjo lacks sufficient knowledge or information to form a belief as to the allegations in Paragraph 23 of the Complaint, and therefore denies those allegations.

24. Honjo admits that PD-1 had been known since the early 1990s. Honjo admits that he provided Wood with cDNA that encoded PD-1. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 24 of the Complaint, and therefore denies those allegations.

25. Honjo admits that PD-L1 is a ligand for PD-1. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 25 of the Complaint, and therefore denies those allegations.

26. Honjo admits that Freeman and Wood filed a provisional patent application on August 23, 1999. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 26 of the Complaint, and therefore denies those allegations.

27. Honjo admits that he has met Freeman, including at GI's offices in Cambridge. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 27 of the Complaint, and therefore denies those allegations.

28. Honjo admits that a meeting took place at GI's offices in Cambridge in the Fall of 1999. Honjo admits that Freeman and Wood had not published any work demonstrating binding of PD-L1 to PD-1 as of the Fall of 1999. Honjo denies the remaining allegations of Paragraph 28 of the Complaint.

29. Honjo admits that Honjo, Wood, and Freeman met to discuss PD-1 and PD-L1. Honjo denies the remaining allegations in Paragraph 29 of the Complaint.

30. Honjo admits that Freeman provided cDNA for PD-L1. Honjo denies the remaining allegations in Paragraph 30 of the Complaint.

31. Honjo admits that one aspect of his research focused on the role of PD-1 and its ligand in treating autoimmune disease by downregulating the immune response. Honjo denies the remaining allegations in Paragraph 31 of the Complaint.

32. Honjo admits that a Material Transfer Agreement (“MTA”) was executed between Dana-Farber and Honjo. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 32 of the Complaint, and therefore denies those allegations.

33. Honjo admits that he is a co-author on a paper titled “Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation,” J. Exp. Med., October 2, 2000. Honjo admits that drafts of that paper were circulated among the co-authors prior to publication, and comments and suggestions were provided. Honjo denies the remaining allegations in Paragraph 33 of the Complaint.

34. Honjo admits the paper describes the authors’ identification of a ligand to PD-1 and research that followed the identification of PD-L1. Honjo admits the paper states that “[i]n this work, we identify a ligand of PD-1 and demonstrate that this receptor–ligand interaction leads to the inhibition of lymphocyte proliferation.” Honjo admits the paper contains five figures reporting experimental data and he contributed to them. Honjo denies the remaining allegations in Paragraph 34 of the Complaint.

35. Honjo admits the paper titled “Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation,” J. Exp. Med., October 2, 2000, states “PD-L1 is also expressed in some cancers, as three ESTs are from human ovarian tumors. This raises the possibility that some tumors may use

PD-L1 to inhibit an antitumor immune response.” Honjo denies the remaining allegations in Paragraph 35 of the Complaint.

36. Honjo admits that an MTA with Dana-Farber was executed in October 2000 which identified “Anti-human PD-L1 antibody” as the biological material to be provided under the agreement. Honjo admits that he received anti-human PD-L1 antibody from Dana-Farber. Honjo admits that a meeting was held at GI’s offices in the Fall of 2000. Honjo denies the remaining allegations in Paragraph 36 of the Complaint.

37. Honjo admits that he is a co-author on a paper titled “PD-L2 is a second ligand for PD-1 and inhibits T cell activation,” Nature Immunology, March 2001. Honjo admits that drafts of this paper were exchanged among the co-authors prior to publication and comments and suggestions were provided. Honjo also admits the paper states “[b]ecause PD-L1 and PD-L2 can inhibit effector T cell proliferation and cytokine production, the PD-L-PD-1 pathway may be an attractive therapeutic target. Blocking the PD-1 pathway may enhance anti-tumor immunity, whereas stimulating this pathway may be useful for down-regulating ongoing immune responses in transplant rejection and autoimmune and allergic diseases.” Honjo denies the remaining allegations in Paragraph 37 of the Complaint.

The Patents

38. Honjo denies that Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in Paragraph 38 of the Complaint.

39. Honjo denies that Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in Paragraph 39 of the Complaint.

40. Honjo admits that Claim 1 of the ’048 patent is directed to “A method for treatment of cancer, wherein a pharmaceutically effective amount of completely human anti-PD-

1 antibody is parenterally administered to a subject with cancer in which PD-L1 or PD-L2 is over-expressed, postoperatively.” Honjo denies the remaining allegations in Paragraph 40 of the Complaint.

41. Honjo denies that Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in Paragraph 41 of the Complaint.

42. Honjo admits that Claim 1 of the ’179 patent is directed to “A method of treating a PD-L1-expressing tumor, comprising administering a pharmaceutically effective amount of an anti-PDL1 antibody to a patient in need thereof, in combination with a pharmaceutically effective amount of one or more chemotherapy drugs, wherein said one or more chemotherapy drugs are selected from the group consisting of an alkylating agent, a nitrosourea agent, an antimetabolite, an antitumor antibiotic, an alkaloid derived from a plant, a topoisomerase inhibitor, a hormone therapy medicine, a hormone antagonist, an aromatase inhibitor, a P-glycoprotein inhibitor and a platinum complex derivative.” Honjo denies the remaining allegations in Paragraph 42 of the Complaint.

43. Honjo denies that Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in Paragraph 43 of the Complaint.

44. Honjo admits that Claim 1 of the ’474 patent is directed to “A method for treatment of a tumor in a patient, comprising administering to the patient a pharmaceutically effective amount of an anti-PD-1 monoclonal antibody.” Honjo denies the remaining allegations in Paragraph 44 of the Complaint.

45. Honjo denies that Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in Paragraph 45 of the Complaint.

46. Honjo admits that Claim 1 of the '999 patent is directed to "A method of treating a lung cancer comprising administering a composition comprising a human or humanized anti-PD-1 monoclonal antibody to a human with the lung cancer, wherein the administration of the composition treats the lung cancer in the human." Honjo admits that Claim 19 of the '999 patent is directed to "The method of claim 1, wherein the lung cancer expresses PD-L1." Honjo denies the remaining allegations in Paragraph 46 of the Complaint.

47. Honjo denies that Shiro Shibayama is or was his colleague at Kyoto University. Honjo admits the remaining allegations in Paragraph 47 of the Complaint.

48. Honjo admits that Claim 1 of the '994 patent is directed to "A method of treating a metastatic melanoma comprising intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in solution to a human with the metastatic melanoma, wherein the administration of the composition treats the metastatic melanoma in the human." Honjo admits that Claim 14 of the '994 patent is directed to "The method of claim 1, wherein the metastatic melanoma expresses PD-L1." Honjo denies the remaining allegations in Paragraph 48 of the Complaint.

49. Honjo admits the Patents disclose experiments by Honjo and colleagues using antibodies that block PD-1 or PD-L1 to inhibit the function of the PD-1/PD-L1 pathway and thereby suppress tumor proliferation. Honjo denies the remaining allegations in Paragraph 49 of the Complaint.

50. Honjo denies the allegations in Paragraph 50 of the Complaint to the extent they relate to the subject matter claimed in the Patents.

51. Honjo denies the allegations in Paragraph 51 of the Complaint.

52. Honjo denies the allegations in Paragraph 52 of the Complaint.

53. Paragraph 53 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 53 of the Complaint.

54. Paragraph 54 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 54 of the Complaint.

55. Honjo denies the allegations of Paragraph 55 of the Complaint.

56. Honjo admits that Dana-Farber purportedly seeks an order correcting inventorship of the Patents, but denies that such an order should issue. Honjo lacks sufficient knowledge or information to form a belief as to the remaining allegations in Paragraph 56 of the Complaint, and therefore denies those allegations.

Count I
(Correction of Inventorship of United States Patent No. 7,595,048)

57. Honjo restates and incorporates by reference its answers to the allegations contained in Paragraphs 1 – 56 as set forth fully herein.

58. Honjo denies the allegations in Paragraph 58 of the Complaint.

59. Paragraph 59 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 59 of the Complaint.

Count II
(Correction of Inventorship of United States Patent No. 8,168,179)

60. Honjo restates and incorporates by reference its answers to the allegations contained in paragraphs 1 – 59 of the Complaint as set forth fully herein.

61. Honjo denies the allegations in Paragraph 61 of the Complaint.

62. Paragraph 62 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 62 of the Complaint.

Count III
(Correction of Inventorship of United States Patent No. 8,728,474)

63. Honjo restates and incorporates by reference its answers to the allegations contained in paragraphs 1 – 62 of the Complaint as set forth fully herein.

64. Honjo denies the allegations in Paragraph 64 of the Complaint.

65. Paragraph 65 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 65 of the Complaint.

Count IV
(Correction of Inventorship of United States Patent No. 9,067,999)

66. Honjo restates and incorporates by reference its answers to the allegations contained in Paragraphs 1 – 65 of the Complaint as if set forth fully herein.

67. Honjo denies the allegations in Paragraph 67 of the Complaint.

68. Paragraph 68 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 68 of the Complaint.

Count V
(Correction of Inventorship of United States Patent No. 9,073,994)

69. Honjo restates and incorporates by reference its answers to the allegations contained in Paragraphs 1 – 68 of the Complaint as if set forth fully herein.

70. Honjo denies the allegations in Paragraph 70 of the Complaint.

71. Paragraph 71 of the Complaint contains conclusions of law to which no response is required. To the extent that a response is deemed required, Honjo denies the allegations in Paragraph 71 of the Complaint.

PRAYER FOR RELIEF

Honjo denies that Dana-Farber is entitled to any relief.

AFFIRMATIVE DEFENSES

Honjo asserts the following affirmative defenses in opposition to the cause of action and allegations of the Complaint. Honjo reserves the right to add additional affirmative defenses as they are learned through discovery and further investigation.

First Defense

(Failure to State a Claim)

72. The Complaint fails to state a claim upon which relief can be granted.

Second Defense

(Inventorship is Proper)

73. The Patents are presumed valid and, with that, the named inventors of the Patents are presumed correct. Freeman and Wood did not invent or contribute to the conception of the inventions contained in the Patents.

Third Defense

(Laches, Acquiescence, Waiver)

74. Plaintiff is not entitled to relief because of laches, acquiescence, waiver, and/or other applicable doctrines.

Fourth Defense

(Exceptional Case)

75. This case is exceptional under 35 U.S.C. § 285. Honjo is entitled to an award of its attorneys' fees and costs incurred in connection with defending and prosecuting this action.

Fifth Defense
(Failure to Join an Indispensable Party)

76. Ono Pharmaceutical Co., Ltd. is a co-owner of the patents at issue and an indispensable party in this case. The Complaint states no basis for jurisdiction, and this Court does not have jurisdiction over Ono Pharmaceutical Co., Ltd. The Complaint must be dismissed for failure to join an indispensable party.

Additional Affirmative Defenses

77. Honjo reserves the right to assert additional defenses as they become known through further investigation and discovery.

PRAYER FOR RELIEF

WHEREFORE, Honjo prays for relief as follows:

- A. Dismissing the Amended Complaint with prejudice, and denying all relief sought in the Amended Complaint;
- B. Judgment in his favor for all claims for relief;
- C. A declaration that this case is exceptional pursuant to 35 U.S.C. § 285, and an award of attorneys' fees and costs; and
- D. For an award of such other and further relief as the Court may deem just and proper.

Respectfully submitted,

Dated: December 21, 2015

/s/ Kelli J. Powell

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Counsel for Tasuku Honjo, E. R. Squibb & Sons, L.L.C. and Bristol-Myers Squibb Co.

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the above document, filed through the ECF system, will be sent electronically to the registered participants of record as identified on the Notice of Electronic Filing on December 21, 2015.

/s/ Kelli J. Powell
Kelli J. Powell (BBO #682079)